CHRONIC TOXICITY SUMMARY

METHYL ETHYL KETONE

(2-Butanone; 3-butanone; ethyl methyl ketone)

CAS Registry Number: 78-93-3

I. Chronic Reference Exposure Level

Inhalation reference exposure level	**500 µg/m^3 (200 ppb)**
Critical effect(s)	Decreased motor nerve conduction velocity in humans
Hazard index target(s)	Nervous system (peripheral)

II. Physical and Chemical Properties (HSDB, 1999)

Description	Colorless gas
Molecular formula	C_4H_8O
Molecular weight	72.10
Density	0.805 g/mL @ 20° C
Boiling point	79.6°C
Melting point	–86.3°C
Vapor pressure	77.5 torr @ 20° C
Solubility	Soluble in alcohol, ether, acetone, benzene and water
Conversion factor	1 ppm = 2.94 mg/m^3 @ 25° C

III. Major Uses and Sources

Methyl ethyl ketone (MEK) is a solvent often found in mixtures with acetone, ethyl acetate, n-hexane, toluene or alcohols. MEK has applications in the surface coating industry and in the dewaxing of lubricating oils. MEK is utilized in the manufacture of colorless synthetic resins, artificial leather, rubbers, lacquers, varnishes, and glues (HSDB, 1993). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California, based on the most recent inventory, were estimated to be 431,645 pounds of MEK (CARB, 1999a). Statewide monitored median and mean concentrations of methyl ethyl ketone have been declining; decreasing from 0.7 and 0.87 ppb in 1992 to 0.05 and 0.12 ppb in 1996 (CARB, 1999b).

IV. Effects of Human Exposures

Few reports of chronic human exposure to MEK were located in the literature. Peripheral neuropathy is described in case reports of workers occupationally exposed to mixtures of organic solvents including MEK (Dyro, 1978; Billmaier *et al.*, 1974). Available animal data suggest a possible synergistic action between MEK and some organic solvents.

A 38 year-old worker was exposed to paint base consisted primarily of toluene and methyl ethyl ketone solvent in an enclosed, unventilated garage (Welch *et al*., 1991). Nausea, headache, dizziness, and respiratory difficulty were first noted, and over the next several days impaired concentration, memory loss, an intention tremor, gait ataxia, and dysarthria. Brain MRI and EGG were normal initially, but later MRIs indicated fluid accumulation over the left parietal area. The condition was diagnosed as toxic encephalopathy with dementia and cerebellar ataxia. Some cognitive, motor and behavioral deficits persisted over 2 1/2 years following the acute exposure.

Neurotoxic effects of MEK were evaluated in 41 exposed workers from a cable factory in Romania (Mitran *et al.*, 1997). Exposed workers prepared a lacquer containing MEK to coat cables. Exposure levels ranged from 149 to 342 mg/m^3. The workers were compared to 63 controls matched for age, physical effort at work, shift, and socioeconomic factors. The mean length of exposure was 14 ± 7.5 years. Subjects completed a questionnaire about anamnesis, a clinical examination, motor nerve conduction velocity tests, and some biochemistry tests. Ocular and upper respiratory tract irritation was more common in exposed than in control workers. The authors indicated a higher frequency of mood disorders, irritability, memory difficulties, sleep disturbance and headache relative to controls. No statistical analysis of these subjective reports was provided. Motor nerve conduction velocity, measured in the median, ulnar and peroneal nerves, was slower in the exposed workers ($p < 0.05$) than in controls.

V. Effects of Animal Exposures

Chronic respiratory disease was observed in rats of all groups exposed to 1254, 2518, or 5041 ppm MEK 6 hours per day, 5 days per week for 90 days (Cavender *et al.*, 1983; Toxigenics, 1981). General histological examination was performed on 10 animals from each exposure group and neuropathologic examination was performed on the remaining 5 animals from each exposure group. A high prevalence of nasal inflammation was observed in all exposure groups and in controls; the authors therefore suggest that the pulmonary lesions were a result of mycoplasma infection although no infectious agent was cultured. Increased relative kidney and liver weights were observed in rats exposed to 5041 ppm MEK, but not at 2518 ppm. Female rats exposed at the highest level also exhibited an increase in serum alkaline phosphatase levels. No pulmonary or neurologic functional tests were conducted.

No adverse effects were observed in pregnant rats exposed to 1126 or 2618 ppm MEK 7 hours per day on days 6-15 of gestation (Schwetz *et al.*, 1974). A statistically significant increase in the number of litters with fetuses with skeletal anomalies was observed in the offspring of the

exposed rats as compared to controls. No single soft tissue anomaly was observed at a statistically significant increased incidence.

Five male Wistar rats were exposed to MEK via inhalation for 8 hours per day, 7 days per week over 15 weeks (Altenkirch et al., 1978). The initial concentration of 10,000 ppm MEK was reduced to 6000 ppm after several days because of severe irritation of the upper respiratory tract. Two other groups of five rats were exposed to 10,000 ppm n-hexane or a 8900 ppm hexane/1100 ppm MEK mixture. The mixture was considered most neurotoxic. The MEK group died suddenly without developing neurological symptoms at 7 to 8 weeks of exposure. The hexane-exposed animals developed paresis by 8 weeks progressing to severe paresis in 1 to 3 of 5 animals between 8 and 15 weeks of exposure. Those exposed to the mixture were much more susceptible to neurotoxic effects, developed effects earlier, and had more severe outcomes. MEK (100 to 1000 ppm) potentiated effects of n-hexane (400 to 9000 ppm) on alveolar epithelia of male Wistar rats exposed for 8 hours/day for up to 89 days (Schnoy *et al*., 1982). MEK also strongly potentiated peripheral and central neurotoxicity of n-hexane in chronic inhalation studies in rats (Altenkirch *et al*., 1979). Urinary levels of the neurotoxic hexane metabolite 2,5-hexanedione increased in male Wistar rats exposed for 12 h/day, 6 days/week over 4 weeks to 2000-ppm n-hexane plus 200 ppm MEK compared with rats exposed to 2000-ppm n-hexane alone (Ichihara *et al*., 1998). Motornerve conduction velocity decreased and distal latency increased in the coexposed group.

Schwetz *et al.* (1991) exposed groups of about 30 Swiss CD-1 pregnant mice to 0, 400, 1000, or 3000 ppm MEK 7 hours per day on days 6-15 of gestation. A slight, statistically significant increase in maternal liver weight was observed in the 3000 ppm exposure group. No overt signs of maternal toxicity were observed. Decreased fetal body weight was observed following maternal exposure to 3000 ppm MEK. The reduction in fetal body weight was statistically significant in male offspring only. Cleft palate, fused or missing sternebrae and syndactyly were observed at low incidences in all groups other than controls. There was also a significant trend for increased incidence of misaligned sternebrae.

Possible synergistic effects of combined exposures to MEK and n-hexane were examined in groups of 8 rats exposed to 100 ppm n-hexane, 200 ppm MEK, 100 ppm n-hexane plus 200 ppm MEK, or fresh air in a chamber for 12 hours per day for 24 weeks (Takeuchi *et al.*, 1983). Motor nerve conduction velocity (MCV), distal motor latency (DL), and mixed nerve conduction velocities (MNCVs) were measured at 0, 4, 8, 12, 16, 20, and 24 weeks of exposure. After 4 weeks of exposure, rats in the 200 ppm MEK groups exhibited significant increases in MCV and MNCV and a significant decrease in DL. No significant differences were observed in subsequent weeks in this exposure group. In the 100 ppm n-hexane group, a significant decrease was observed in DL after 4 weeks and a slight non-significant decrease was observed in MNCV after 24 weeks. Rats exposed to 100 ppm n-hexane plus 200 ppm MEK exhibited significant decreases in MCV and MNCV after 20 and 24 weeks of exposure, which suggested that mixed exposure to n-hexane and MEK may be more toxic than n-hexane alone.

VI. Derivation of Chronic Reference Exposure Level

Study	Mitran *et al.* (1997).
Study population	workers from a cable factory in Romania
Exposure method	Occupational exposure (inhalation)
Critical effects	Decreased motor nerve conduction velocity
LOAEL	149 mg/m^3 (51 ppm)
NOAEL	None
Exposure continuity	8 hours/day; 5 days/week (assume inhaled 10 m^3 during work shift, of total 20 m^3/d)
Average experimental exposure	53-122 mg/m^3 (18-42 ppm)
Human equivalent concentration	53 mg/m^3 (18 ppm)
Exposure duration	14 ± 7.5 years.
LOAEL uncertainty factor	10
Subchronic uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Chronic inhalation reference exposure level (REL)	0.2 ppm (200 ppb; 0.5- mg/m^3; 500 µg/m^3)

The Mitran study was selected as the REL key study because it is the only available epidemiological study in which exposure to MEK alone was reported for one of the groups examined. Workers were exposed to measured concentrations of 149 - 342 mg/m^3 MEK during an 8-hour shift. Exposed workers showed statistically significant ($p < 0.05$) reductions in nerve conduction velocity. A NOAEL was not determined in this study.

The study in rats by Cavender *et al.* reported both NOAEL and LOAEL concentrations following subchronic inhalation exposure. Average human equivalent concentration for the NOAEL group in this study was 450 ppm. Application of a total uncertainty factor of 100 (subchronic, 3; interspecies 3 + RGDR= 1.0; intraspecies 10) indicates a REL of 4 ppm (10 mg/m^3) based on this study.

Evaluation of the study by Schwetz *et al.* (1991) suggests that developmental effects may occur at slightly higher concentrations. A developmental NOAEL of 1000 ppm from this study yields an HEC of 292 ppm (1000 ppm x 7 hrs/24 hrs x RGDR of 1). Using a 3-fold interspecies uncertainty factor and a 10-fold intraspecies uncertainty factor, a REL from this study of 10 ppm (30,000 µg/m^3) was derived.

In the study by Altenkirch *et al.* (1978), Wistar rats were exposed to 6,000 ppm for 7 to 8 weeks. A frank effect level of 6000 ppm was observed, from which an HEC of 2000 ppm (6000 x 8hrs/24 hrs x RGDR of 1) can be derived. Applying a 10-fold LOAEL uncertainty factor, a 3-fold subchronic uncertainty factor, a 3-fold intraspecies uncertainty factor, and a 10-fold intraspecies uncertainty factor, a 2 ppm value is obtained. If an additional 10-fold severity factor

were applied, a 200 ppb (600 µg/m^3) REL is thus derived. However, frank effect levels are generally inappropriate for risk assessment, as the difference between such a level and a LOAEL is uncertain. The lethality of Wistar rats in this study is notable, given the observed NOAEL at 2518 ppm and relatively mild effects at 5041 ppm in F344 rats exposed for 90 days (Cavender *et al*., 1983). This suggests that (1) Wistar rats are more susceptible than F344 rats to subchronic effects of MEK inhalation and/or (2) there is a narrow range between toxicity and lethality for MEK. The difference between 8 hr/day, 7 days/wk exposures and 6 hr/day, 5 days/wk may also be significant.

VII. Data Strengths and Limitations for Development of the REL

The health effects database for MEK is extensive, though not all the data are suitable for use in risk assessment. Most of the epidemiological studies and many of the experimental animal exposure studies involve mixed solvent exposures. However, the study reported by Mitran *et al.* (1997) included a group exposed to MEK alone. Short-term controlled human exposures have shown MEK to be an acute irritant gas at concentrations as low as 200 ppm (Dick *et al*., 1992). Long duration sudies of pure MEK inhalation exposures have been reported by Cavender *et al*. (1983) and Altenkirch *et al*. (1978) with rats.

The major strength of the REL for MEK is the use of a measured parameter in exposed humans as the end point.. The major uncertainties are the failure to observe a NOAEL, and some uncertainties in the quantitation of exposure.

U.S. EPA developed an RfC for methyl ethyl ketone in 1992 (U.S. EPA, 1994a) but the methdology used has been superseded (U.S. EPA, 1994b) and the U.S. EPA has not revised the RfC as of May 1999.

The proposed REL based on human exposures is substantially lower than those levels based on animal studies. However, the most suitable animal study, by Cavender *et al.* (1983), is only a subchronic (90 day) study, and it does not appear that the specific functional neurological parameters found to be affected in exposed humans were measured in the experiment in rats. Also the toxicity data in rats show some indications of concern, particularly the possibility of lethal effects at relatively modest doses, and large inter-strain differences, implied by the Altenkirch *et al.* (1978) study.

VIII. References

Altenkirch H, Stoltenburg G, Wagner HM. 1978. Experimental studies on hydrocarbon neuropathies induced by methyl-ethyl-ketone (MEK). J. Neurol. 219(3):159-170.

Altenkirch H, Stoltenburg-Didinger G, Wagner HM. 1979. Experimental data on the neurotoxicity of methyl-ethyl-ketone (MEK). Experientia 35(4):503-504.

Billmaier D, Yee HT, Allen N, Craft B, Williams N, Epstein S, Fontaine R. 1974. Peripheral neuropathy in a coated fabrics plant. J. Occup. Med. 16(10):665-671.

CARB (California Air Resources Board). 1999a. Air toxics emissions data collected in the Air Toxics Hot Spots Program CEIDARS Database as of January 29, 1999.

CARB. 1999b. 1990-1996 Statewide Methyl Ethyl Ketone Summary, ppb. WWW document (http://www.arb.ca.gov/aqd/mek/mkstate.htm).

Cavender FL, Casey HW, Salem H, Swenberg JA, and Gralla EJ. 1983. A 90-day vapor inhalation toxicity study of methyl ethyl ketone. Fundam. Appl. Toxicol. 3(4):264-270.

Dick RB, Krieg EF Jr, Setzer J, Taylor B. 1992. Neurobehavioral effects from acute exposures to methyl isobutyl ketone and methyl ethyl ketone. Fundam. Appl. Toxicol. 19(3):453-473.

Dyro M. 1978. Methyl ethyl ketone polyneuropathy in shoe factor workers. Clin. Toxicol. 13(3):371-376.

HSDB. 1999. Hazardous Substance Data Bank. National Library of Medicine, Bethesda, Maryland. WWW database (http://sis.nlm.nih.gov/sis1/).

Ichihara G, Saito I, Kamijima M, Yu X, Shibata E, Toida M, Takeuchi Y. 1998. Urinary 2,5-hexanedione increases with potentiation of neurotoxicity in chronic coexposure to n-hexane and methyl ethyl ketone. Int. Arch. Occup. Environ. Health 71(2):100-104.

Mitran E, Callender T, Orha B, Dragnea P, Botezatu G. 1997. Neurotoxicity associated with occupational exposure to acetone, methyl ethyl ketone, and cyclohexanone. Environ. Res. 73(1-2):181-188.

Schnoy N, Schmidt R, Altenkirch H, Wagner HM. 1982. Ultrastructural alteration of the alveolar epithelium after exposure to organic solvents. Respiration 43(3):221-231.

Schwetz BA, Leong BKJ, and Gehring PJ. 1974. Embryo- and fetotoxicity of inhaled carbon tetrachloride, 1,1-dichloroethane and methyl ethyl ketone in rats. Toxicol. Appl. Pharmacol. 28:452-464.

Schwetz BA, Mast TJ, Weigel RJ, Dill JA, Morrrissey RE. 1991. Developmental toxicity of inhaled methyl ethyl ketone in Swiss mice. Fundam. Appl. Toxicol. 16:742-748.

Takeuchi Y, Ono Y, Hisanaga N, Iwata M, Aoyama M, Kitoh J, and Sugiura Y. 1983. An experimental study of the combined effects of n-hexane and methyl ethyl ketone. Br. J. Ind. Med. 40:199-203.

Toxigenics 1981. 90-Day vapor inhalation toxicity study of methyl ethyl ketone in albino rats. Submitted to Chemical Industry Institute of Toxicology, Research Triangle Park, NC. Doc ID 878212064, Microfiche No. 205953. [cited in U.S. EPA, 1994].

U.S. EPA. 1994a. U. S. Environmental Protection Agency. Integrated Risk Information System (IRIS). Cincinnati, OH: Office of Health and Environmental Assessment, Environmental Criteria Assessment Office.

U.S. EPA. 1994b. U.S. Environmental Protection Agency Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. EPA/600/8-90/066F. Washington, DC: Office of Research and Development,.

Welch L, Kirshner H, Heath A, Gilliland R, Broyles S. 1991. Chronic neuropsychological and neurological impairment following acute exposure to a solvent mixture of toluene and methyl ethyl ketone (MEK). J. Toxicol. Clin. Toxicol. 29(4):435-445.